REMARKS

Reconsideration is requested.

Claims 1, 3-7, 10, 11, 14, 15, 17-25 and 28-31 are pending.

New claims 28 to 31 relating to methods to produce the glutamine-auxotrophic human cell of any one of claims 1 to 6; 17, 18, 21 and 22 are supported by the originally-filed specification and claims, such as in the description on page 7, 1st and 2nd full paragraphs (transfection), page 9, last paragraph and page 11, lines 17 – 20 (culture medium). Further support is provided in particular by Examples 6 and 7. No new matter has been added.

To the extent not obviated by the above amendments, the Section 112, second paragraph, rejection of claims 14, 15, 17, 18 and 21-24, is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following comments.

Claims 14, 17, 21 and 23 have been revised to refer to a pending claim.

Withdrawal of the Section 112, second paragraph, rejection is requested.

The Rule 75 objection of claims 25 and 26 is moot in view of the cancellation of the same above.

The Section 103 rejection of claims 1, 3-7, 10, 11, 19, 20, and 25-27 over Bebbington (U.S. Patent No. 5,891,693) "as evidenced by" Barsomian (U.S. Patent No. 5,238,821) in view of Brandt (U.S. Patent No. 6,395,484), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to believe that Bebbington et al. teaches the following:

- the use of mouse and rat lymphoid cells lines; in particular, the use of NSO cells;

- the use of glutamine-synthetase (GS) as selection / amplification marker; or

- the expression of heterologous proteins such as a B72.3 chimeric antibody.

The Examiner is further understood to appreciate that Bebbington et al. does not teach:

- the use of human glutamine-auxotrophic cell; or

- the production of sialylated proteins or

- a cell culture method using serum-free medium.

The Examiner is also understood to assert that it would have allegedly been obvious to the ordinarily skilled artisan to have modified the teaching of Bebbington et al. from making and using a rodent glutamine auxotrophic cell to making and using a human glutamine auxotrophic cell as taught by Brandt el al. to produce an exogenous sialylated protein.

Brandt et al. is understood to teach the following:

- the use of human glutamine auxotrophic cells (HT1080);

- the use of serum free medium;

- the use of selection / amplification marker such as DHFR; and

- the production of glycosylated proteins (such as EPO) comprising sialic acid moieties.

Clarification is requested in the event the rejection over the combination of cited art is maintained as the applicants believe that the cells as described in Bebbington et al. and when compared to the cells as claimed in the present application have only the presence of GS and the expression of a heterologous proteins in common (as outlined above).

The applicants therefore consider Brandt et al. as perhaps being the closest prior art, which would not have made the claimed invention obvious. Specifically, as outlined above, Brandt et al. discloses the use of human glutamine auxotrophic cells such as HT1080; the use of serum free medium; the use of a selection / amplification marker such as DHFR to produce glycosylated proteins (such as EPO) comprising sialic acid moieties. It should however be noted that Brandt et al. does not actually show glycosylation or the presence of sialic acid moieties. Thus, a difference between Brandt et al. and the claimed invention is the presence of the additional selection marker GS in the cell.

The effect of the presence of GS in said human glutamine auxotrophic cell - according to the claimed invention - is not only the ability of the cell to grow in glutamine free medium, but most importantly is the cell's ability to exhibit elevated specific rates of protein synthesis, improved protein activity, enhancement of the protein quality (such as enhanced sialylation) and extended cell viability. These additional effects of GS were clearly surprising and have not been anticipated or rendered obvious by any of the cited prior art documents including Bebbington et al.

In detail: Examples 6, 8 and 11 of the present application show that the HT1080 human cell line transfected with EPO and DHFR gene (named R223; Example 1 – *R223*

which is used as starting point for the present invention is thus similar to the cell line as described by Brandt et al.) and supertransfected with GS exhibited elevated specific rates of EPO synthesis compared to the R223 cell line (Table 5 – growth of cells in medium with serum; and Table 7 and 12 – growth of cells in serum-free suspension culture).

Further, examples 9 and 11 of the present application show that the EPO produced by the GS supertransfected cell exhibited intensification of the more acidic isoforms when compared to the EPO produced by the R223 cell line, which indicates an increased degree of sialylation of EPO produced by the GS supertransfectant cell line (page 27, line 4 to 5 of WO 03/054172) – while the more acidic bands possess the highest biological activity (page 28, line 1).

Still further, Example 10 of the present application shows that the cell line supertransfected with GS has extended cell viability and thus, an increase in duration of culture resulting in an increase in product concentration (Table 11).

None of these effects of GS have described or remotely suggested by Bebbington et al. or Barsomian et al. Thus, the person ordinarily skilled in the art would not have envisaged to transfect the glutamine-auxotropic human cell stably expressing EPO with the help of the DHFR selection marker – as, for example, disclosed in Brandt et al. - with the additional GS marker – the GS marker only being disclosed for example in Bebbington et al. – to produce a product with improved cell viability and product quality such as glycosylation.

The claims invention is submitted to be patentable over the cited combination of art and withdrawal of the Section 103 rejection is requested.

For completeness, the applicants note the Examiner's comment on page 11 of the Office Action dated July 25, 2007, that the claims do not reflect the requirements of supertransfection with GS or of enhanced sialylation. The applicants note in response that although the term "supertransfection with GS" is not explicitly mentioned in the claim, the presence of GS in addition to another selection marker such as DHFR is clearly a feature of the claims. New claims 28 to 31 further emphasize the step of "supertransfection", i.e. the additional transfection of GS selection marker gene. As regards to the enhanced sialylation, the applicants note that claims 1 and 7 require a "sialylated" protein, and that the enhancement of sialylation is a direct consequence of using the claimed cell or process according to the claims.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required.

Respectfully submitted,

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